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Remarks on the Pathology of Jaundice

Preface

The following Dissertation does not contain anything original on the Pathology of Jaundice, but is rather a Review of the different opinions on the subject held at the present time and a Discussion of the theories of Bucal, Harley, Freunds and Kühne.

In this, as in all other subjects of investigation, different observers have come to hold very different opinions; and what renders the subject more difficult, is the fact that the same experiment in the hands of different experimenters seem to have led to opposite results.
Chapter I

The yellow coloring of the skin and conjunctivae, to which the terms Jaundice, Icterus, Morbus Regius elicit have been applied, occurs in a great variety of diseases, diseases not only of the liver and its appendages, but also of various other organs, and of the system generally. Jaundice is only a symptom, although from the great and not advantageous change it makes in the appearance, it is apt to be looked upon by the unpro-fessional as the disease, their most urgent wish being to regain their natural complexion as soon as possible.

This yellowness of the skin and conjunctiva is ascribed to the coloring matter of the bile being present in the blood and staining the tissues. The tint of the skin varies from
A pale yellow to a dark green, this variation depending, among other things, on the amount of coloring matter, and the age and complexion of the patient. The jaundice lasts some time after the cause has been removed, longer, Cérisier paranite, in old than in young people.

Other tissues are involved, more or less, in addition to those already mentioned. When the jaundice is due to some obstruction to the flow of the bile through the ducts provided for its excretion, the liver is very deeply stained, but when the jaundice is due to some other cause the liver is not much stained.

"The biliary pigment seems also fixed in an especial manner in the adipose cellular tissue, as if there were some affinity between the colouring matter of bile and fatty substances. In some races,
Indeed, the fat is naturally of an orange color. It is so in the cows of Guernsey; and I have more than once remarked it in Negroes from the West Coast of Africa, who were not jaundiced.” (1)

Dr. Budd says that the lungs and kidneys are not colored; this seems to be correct as far as the lungs are concerned, but in several of the cases of jaundice given by Hirsch, in his "Clinical Treatise on Diseases of the Liver", the kidneys were found to be colored sometimes yellow, sometimes olive green. He says that this occurs in persistent and severe cases of jaundice. Considering that the kidneys afford one great channel by which this abnormal coloring matter is removed from the blood, I should think it probable that these organs would frequently par-

Note 1. Diseases of the Liver. Dr. Budd.
Tealicate in the general coloring.

The dura mater may be yellowish in cases of jaundice but the brain itself very seldom is.

The biliary pigment does not generally attach itself to mucous membranes. In one or two of the cases given by Prof. Luecht, in the work already referred to, the mucous membrane of the pharynx and esophagus was of a yellow color, but cases such as these I should think are rather exceptional.

Various other tissues are liable to this coloring, as for example the bones and teeth and serous and fibrous membrane. It is even said that the foetus in utero may become jaundiced, if there be a long continuance of the disease in the mother.

The biliary pigment is also found in some of the secretions. It is excreted partly by the kidneys, the urine generally having a saffron
color and tingeing any white substance. It is also excreted in considerable quantity by the glands of the skin, sometimes so as to stain the linen yellow. It is present in serous effusions into the different cavities, Prof. Fuchs says earlier in these than in the urine and sweat. Some authorities hold that bilary pigment is sometimes present in mucus, Fuchs says that it never is, but that it is present in all mucous or serous excretions, and hence that the expectoration in bilious pneumonia may be colored yellow. The presence of the pigment in mucus would, I should think, stain the mucous membranes more or less, but these membranes are very seldom found yellow, and the yellowness of the expectoration can be explained by the presence of exudation matter in it. The tears and the milk have also been found to contain bile-pigment.
Dr. Saunders says that the eyes and roots of the nails first become yellow afterwards the whole body, Ferdinand that "the colour is first observed in those places where the epidermis is thin, and the secretion is abundant, upon the alae of the nose, at the angles of the mouth, upon the forehead and neck. Sometimes (he says) I have seen the upper half of the body very distinctly tinged without any change being visible on the lower."
Chapter II

Dr Budd classifies the production of jaundice under two heads. He says "Jaundice may be produced in two ways; 1st by some impediment to the flow of bile into the duodenum, and the consequent absorption of the retained bile; and 2nd by defective secretion on the part of the liver, so that the principles of the bile are not separated from the blood."

Dr Harley's classification is the same viz that "the pathalogy of jaundice may be embodied under two heads jaundice from suppression of the biliary function, and jaundice from reabsorption of the secreted but retained bile." (1)

Prof Ferriehs differs from the two preceding authors. He gives three causes of jaundice.

Note 1 Dr Ferriehs by Dr Harley
"Obstruction to the escape of bile"

"2nd Diminished circulation of blood in the liver, and consequent abnormal diffusion"

"Both of these conditions give rise to an increased imbibition of bile into the blood, and in both cases the liver is more or less directly implicated."

"Through some alteration in the substances contained in the blood."

On one point all are agreed, viz., that jaundice does arise in some cases from absorption of the bile, to the excretion of which by the proper channels, some impediment has arisen, and the majority of cases of jaundice have this source, and will form the subject of this chapter.

"Obstruction to the passage of the secreted bile into the duodenum having arisen, the biliary coloring matter is taken into the blood by two channels, by the lymphatics and
by the hepatic veins.

To prove the absorption by the lymphatic, Saunders tied the hepatic duct of a dog; two hours afterwards, the lymphatics connected with the liver were found distended with a fluid of a bileous color, and they could be traced to the thoracic duct, the contents of which were only moderately bileous. To prove that the bile also enters the hepatic veins Dr. Saunders made another experiment. A second dog was procured, and a ligature made on the hepatic duct as in the preceding experiment. Two hours after blood was taken from the jugular vein, and set to rest, in order that it might separate into its serume and crassamentum. The liver was then drawn down a little from the diaphragm, and blood taken from one of the hepatic veins. This blood as well as the former was allowed to separate into parts, and on immersing pieces
of white pus into the lumina of cub. that taken from the hepatic veins gave the deeper tinge, the other produced only a very slight degree of discoloration. This entrance of the bile into the hepatic veins, described by Saunders simply to repulsion is more elaborately explained as follows by Prof. Frerichs. The bile secreted by the cells of the liver enters the commencement of the bile ducts by filtration, and the sugar also secreted by the cells of the liver enters the veins by diffusion. Whatever view we adopt as to the mode of separation of the substances secreted by the liver, still it is certain, that an increased absorption of the bile into the blood may be dependent on a difference in tension of the contents of the hepatic cells and blood-vessels. Such a condition may arise in two ways: 1, from obstruction of the bile ducts by which pressure on the
Side of the cell contents is increased, and 2, from obstruction to the flow of blood in the portal system, and consequent diminution of the pressure on the side of this fluid."

When therefore the bile is obstructed in its passage to the duodenum, it enters the circulation partly by the lymphatics, and partly by the hepatic veins on account of the tension caused by its accumulation.

There are certain actions of the body, which aid the bile in its passage to the duodenum, and the cessation or impairment of which may assist in causing, if they do not actually cause, the production of jaundice. The respiratory movements of the chest and abdominal muscles have a decided influence in assisting the passage of the biliary secretion along its excretory ducts, and this influence is greater, consequent on the additional pressure, when the stomach is distended with food, which may part-
by explain the increased flow of bile during digestion. Exercise, by increasing the rapidity and force of the respiratory movements, will also increase this assistance. Jaundice is sometimes observed in connection with pneumonia and pleurisy of the right side of the chest, but I think we can scarcely consider the improvement of motion consequent on such disease as a sufficient cause of the latter. It is a general belief, that that unpleasant and traveling companion sea-sickness, although it destroys the sufferer's pleasure, yet improves his biliary system. The excessive action of the muscles must give a great impulse to the bile, and do good if there be any sluggishness in its secretion, of course this applies to the action of any emetic, if sufficiently powerful. The obstructions to the excretion of the bile arise from various sources. They generally exist in the excretory duct external to the liver and near its termina...
Obstruction of the cystic duct will not cause jaundice, neither does filling up, or congenital absence of the gall-bladder. Some of the lower animals normally have no gall-bladder. Obstruction of the cystic duct could only cause jaundice by absorption of the bile contained in the gall-bladder, but this would not be sufficient to cause any perceptible staining of the tissues. There are cases on record of jaundice arising from congenital absence of the bile ducts. This is very rare.

A common cause of obstruction is the impaction of a gall-stone in the ductus communis choledochus. Gallstones, which consist of inspissated bile and choleserine form in the gall-bladder, sometimes in great numbers, and one of these in its passage along the ducts may completely close the channel from its form or size, for they sometimes attain a size very much larger than the caliber of the
ducts. Generally in a shorter or longer time the concretion finds its way into the duodenum, and, the cause being removed, the pain and icterus gradually disappears. Sometimes however the gallstone becomes so impacted that it remains a fixture, and the icterus consequently is permanent and is generally fatal in about a year. Gallstones occur more frequently in women than in men, and in those who follow sedentary occupations, than in those whose employment necessitates active exercise. This may be explained by the fact that females and those who follow sedentary occupations have less active exercise of the bile which active exercise affords, and the consequent comparatively quiet and slow discharge of the bile into the gall-bladder will favor the formation of these bodies, and, since in the gall-bladder the bile loses a portion of its water by absorption, the longer it remains there the less fluid
will it become.

Foreign bodies such as intestinal worms and the stones of fruits are said to have found their way from the intestine into the termination of the ductus communis, and to have obstructed the flow of bile. This is however comparatively rare, and considering the oblique course of the duct through the wall of the intestine, one can scarcely understand how it occurs at all.

From their anatomical relations the biliary ducts are liable to be compressed by surrounding parts, as by a cancerous or other tumour of the pancreas, by cancer of the pylorus, by an accumulation of fluid in the colon or by the gravel uteri. A tumour on the under surface of the liver will also compress the ducts in that situation, and they are liable to close from what is called adhesive inflammation. The uteri caused
by an accumulation of feces, will in most cases be readily removed, the cause of the jaundice of pregnancy or men will be removed in due time, but that arising from malignant tumours of the pancreas, liver or pylorus will be permanent, the causes being irremediable.

In jaundice from obstruction the liver is at first much increased in size from the distension of the biliary ducts, but if the obstruction be not removed the continued pressure interferes with the secreting power and nutrition of the liver which in consequence gradually becomes atrophied.
Chapter III

Although the majority of cases of icterus can be explained by some mechanical obstruction to the excretion of the secreted bile, yet we often can find no cause of this kind, and sometimes there is even no structural lesion of the liver. Jaundice has been known to occur from fright and other emotions and during the course of pneumonia, pyemia, typhus, intermittent and other fevers, and it sometimes occurs after poisoning with the salts of copper. By older writers it was assumed that spasmotic structure of the ducts was the cause of all those cases of jaundice, for which they could not account by any other obstruction. This is organic muscular fibre in the walls of the ductus communis cholecodothers, but, as Prof. Virchus remarks, the constriction would require to exist three days before it produced jaundice, and
a peculiar structure of the duct lasting for so long a time is, I think, very improbable. But the irritation of a fulctone might cause contraction of the duct around it, hindering its passage and making the closure of the canal more complete.

More recently Dr. Reudel and others have held the view that the bile exists in the blood of the portal vein before it reaches the liver, and that that organ merely filters the bile from the, as the kidneys do the urine, and, that, if any organic lesion or functional disturbance should arise in the liver to impair or destroy its filtering power, the bile accumulates in the blood and is carried on through the system (producing jaundice). This simple and apparently satisfactory theory is not however supported by more recent investigations. The experiment of Magendie, who found that by injecting bile into the portal
...e of a dog, the animal has un-
troubled, but that it was killed when
the bile was injected into one of the
systemic vessels, might be brought
forward in support of this view, as
showing that the liver can filter
prerounded bile from the blood. But,
on the other hand all chemical
examinations of the portal blood
have failed in detecting bile in it.
Animals have been kept alive for
some days and even weeks after the
extirpation of their livers, and then
no trace of bile could be found in
their blood urine or tissues; and
what is more decisive, cases occur of
organic disease of the liver, where we
find its structure so altered, that we
cannot believe that its function could
have been carried on, and yet there
was no icterus; surely in such cases
if the bile existed normally in the

Kirkes' Physiology p. 259.
blood, it would accumulate. From these considerations I consider untenable the theory given above.

A more recent view of the functions of the liver is, that it not only excretes but secretes the bile, that is, that the bile does not exist in the blood sent to the liver, but that it is formed in the liver for the first time. Dr. Harley takes a middle course between this opinion and that previously given. He holds that the glycocholic and taurocholic acids of the bile are formed in the liver, but that the biliverdine is a direct derivative of the coloring matter of the blood, and (I use his words) is not peculiar to the liver or its secretion, but is the product of several organs, and is always to be detected in the blood, independently of the presence or absence of the liver. He holds, therefore, that jaundice arises from defective excretion of part of the bile, namely, the coloring matter. Dr. Harley gives no
facts to support an opinion, which
if correct would very much simplify
the pathology of jaundice. This view
has been strongly objected to by many
recent observers, and, as the differences
of opinion on this cause of production
of icterus things very much on whether
it be the case or not that biliverdin
exists performed in the blood of the
portal vein, it is to be regretted that
Dr. Harley in his recent work on Jaundice
should seem to take this to be an ac-
ccredited fact, not bringing forward any
proofs whatever of the accuracy of his
statement. The objections, formerly given,
to the views held by Dr. Budd apply with
equal force to that of Dr. Harley, rendering
it, I think, quite untenable.

There is left for discussion the theories
of those who hold that the liver does
not filter but secretes the bile from the
blood. These arguments in favor of this
opinion, are very much those given before
as objections to the view, that the bile or
part of it exists in the blood of the portal vein before reaching the liver, and certainly these arguments appear to be very conclusive.

Holding this doctrine some explanation must be given of the production of jaundice with or without structural change of the liver; and first of Fereches theories. The second and third divisions of his classification of the causes of icterus remain to be noticed; postponing the second the third is that icterus arises "through some alteration in the subtle metamorphoses of substances contained in the blood." These "substances contained in the blood" are the colorless bile acids, which Fereches holds may be, and are converted into bile pigment. A certain quantity of these bile acids, he believes, normally enter the circulation, both from the intestines from the liver and from the kidneys, and in the blood under the influence of respiration undergo transformations into bile-pigment and subsequently into
other substances which are excreted by the kidneys, and that, when anything interferes with the completion of their metamorphosis, bile pigment is produced in the blood in sufficient quantity to produce icterus. The principal arguments brought forward in support of this view are: that the bile-acids and bile-pigment never coexist in the urine, in which theory is supported by Lehman, Gross-Besamez, Scherer, and Staudeler; that by the action of concentrated sulphuric acid upon colorless bile, there are formed color-producing substances (Chromogen), which, upon exposure to the atmosphere, and still more rapidly on the addition of nitric acid, exhibit alternations of tints corresponding in every respect with bile-pigment; and that "the same pigments and color-producing substances (Chromogen), which in their properties precisely resemble cholecypheine, are produced by the injection of large quantities of colorless bile into the vascular system.
of living animals. Ferriuchs injected fresh ox bile freed from its coloring matter and mucus into the veins of dogs. There were 29 experiments of this nature, in 19 of these the urine of the dogs, after the injection, coloring matters which gave the chemical reactions of bile-pigment, in the urine of the other 10 no change in the color of the urine was observed. In the urine of none could bile-acid be detected.

Speaking of this doctrine Dr. Harleq says "I have taken no notice of Ferriuchs theory regarding the bile-acids being changed into bile-pigment. I have done so advisedly, feeling as I do, that when that observer investigates the subject more closely, he will himself abandon such an untenable doctrine, founded as it is on an erroneous view regarding the nature of bile-pigment. The colour produced by Sulpfitre Acid is as different in its chemical nature from animal pigments, as any two substances
can possibly be. Indeed, they have no
tend of connection whatever, except the
merit text." It is again to be regretted
that, in thus objecting to Frendel's theory
and experiments, Dr. Harley should con-
tent himself with a mere assertion,
bringing forward no facts in its sup-
port. I do not think anyone can
consider the preceding quotation an
objection to the theory, except as so far
as one may place a higher value on
Harley's than on Frendel's opinion.

It is to be observed that of the twenty-
nine dogs experimented on only nineteen
support the theory, and although this
might be explained, still further experiments
of this nature would be necessary, in order
to have much force. The author, however,
does not I think consider his theory
yet perfected.

Kühne's views on the production of
icterus are different from the preceding,
though they may be considered to a
certain extent a modification of them.
He holds that, bile-acids and bile-coloring-matter exist in icteric urine, in which alone can bile-acids be detected, that bile-acids undergo no metamorphosis in the blood, but are excreted unchanged by the the kidneys, that bile-coloring-matter does appear in the urine after the injection into the circulation of colorless solutions of bile-acids or their salts, that this is explained by the action of these acids on the blood-corpuscles, dissolving the cell-wall, and converting the hematin into bile-pigment; and "that no acetoephelic acid is formed in the liver during jaundice, but tauro- or choleric acid or perhaps only cholodic acid." This he concludes from the fact that benzoic acid found during icterus is excreted in the urine as benzoic acid, not having undergone any change, while

Note (1)

"Contributions to the Pathology of Icterus" by Dr. W. Kühne
"Vandrov's Archives" Abstracted by George Scott M.D.
in Beale's Archives of Medicine Vol I
the presence of glycine either free or in glycine-hydrochloric acid would have changed the terebic into hippuric acid.

The arguments brought forward by Kücher in support of his doctrine are somewhat as follows. "The bile-acids and their salts have the peculiarity property of dissolving the blood-corpuscles." In some of the animals, into whose veins the bile-acids were injected, there was hematuria. A concentrated solution of hemato-globuline was injected into the veins of healthy dogs and generally on the next morning, a tolerably dark-coloured, alkaline, albuminous urine was passed, which showed a reaction, with nitric acid, resembling that of bile-coloring matter, but not proving unequivocally the presence of the latter." - "A dog, that had before only been subjected to an injection of hemato-globuline, had now 15 cubic centimeters of such a solution, with the addition of only 0.5 Cub. Centim. of a 4 per cent. solution of glycodeholate.
of soda injected into the left jugular vein. The urine of the dog and cat contained albumen, and gave a splendid reaction of bile coloring-matter with nitric acid. This experiment was repeated twice with the same result. When the same quantity 0.5 c.c. c.c. of glycolthionate of soda was injected alone into the veins, without the solution of bismuto globulin, the urine of the dog afterwards contained but a trace of bile coloring-matter." Kühne maintains that the large quantity of bile-acids injected by Ferrier's, two, four and five grammes would have rendered the urine perfectly black, he also says, that his experiments were followed, often by sudden death of the animals, or by epileptiform spasms, or, in most cases, by Atmischkeit, apathy and somnolence, while Ferrier only observed after his experiments, sometimes drowsiness or vomiting, but no stupor or convulsions. The effects proc-
duced on the animal generally by the injection into the veins of bile-acids, might have some weight in the consideration of these theories.

It will have been observed that Kühne completely denies the correctness of one of Freich's most important arguments, namely, that bile-acids and biliary pigment never coexist in icteric urine. If this were correct, it certainly would favor Freich's view, as the occasionally appearing at a different, but more at the same time, of these two constituents of the bile, would lead to the supposition that one was somehow derived from the other. Kühne, however, says that he never found bile-acids in normal urine, but that he did so in icteric urine, and he accounts for Freich's not finding them by the insufficiency of his tests. In the Transactions of the Pathological Society Vol xii. p. 107 there is given a case of acute atrophy
of the liver, with jaundice, in which the bilirubin acid was detected in the urine. This point, I think, must still be considered but justice.

There is a doctrine held in considerable favor at present by many animal chemists, namely, that all animal pigments are derived from the hemo-
tine (of the blood). Whether this doctrine be true or not, (and I think that very probably it is true), there seems to be a close relation between the coloring matter of the blood, and that of the bile. In support of this let me quote from Prof. Freiermuth: "This theory has acquired fresh support from the investigations of Vorichow upon pathological pigments. These investigations have proved that, under certain circumstances, a yellow substance is formed from the hemo-
tine, which, in its relation to solvents and reagents, bears a close resem-
blance to cholepyrhrine." - "Junker and Funke have brought forward just.
arguments in favor of the intimate relation subsisting between the bile-pigment and the red matter of the blood, by showing that a modification of the coloring-matter of the bile, viz., biliverdine, can easily be transformed into "hemalorine"—a derivative of "hematin". This would appear to indicate the possibility of a direct transformation of hematin into cholera toxin. These investigations correspond very well with the results of Ruhis's experiments; for although no one has yet, as far as I know, succeeded in obtaining biliverdine directly from hematin, yet we must remember that organic chemistry is still a progressive science, and that the formations and reactions of the bile take place under the influence, not only of chemical, but also of vital forces, which the chemist can imitate very imperfectly in his laboratory. I should like to know what effect bile acids have on hematinic out of
the body, placed in circumstances as similar as possible to the blood of a living animal. The experiment, being so obvious, I cannot but think has been tried, and, as success undoubtedly have been made known, I conclude that it has failed; that is, that the effect of bile-acids on hæmato- 
tinin, out of the body, does not correspond to what is supposed to be the effect in the body; this leading to the sup-
position that other accessory means are necessary for the production of bile-pigment besides bile-acids and hæmato-
tinin. I do not know, when this doctrine was first promulgated, but the following paragraph shows that Soane at least had some idea of it. He says "green and bitter bile being in 
common to all animals with red blood, and found only in such, makes it 
probable that there is some relative 
connection between this fluid, and the 
coloring matter of the blood," by the ed
particles contributing more especially to its formation." Normally, according to this theory, a certain number of the corpuscles are destroyed in the liver, the bile-acids being first located and then acting on the corpuscles, causing the cell-wall and transforming the hemoctene into biliverdine.

I think that the preponderance of evidence is in favor of the views of Dr. P. Kühne, though I should by no means be understood to say that he has proved his case. Additional investigations, and a more extended knowledge both of animal chemistry and of animal physiology are necessary for its full completion.

Here is yet another explanation of the production of jaundice. Freichs' second cause is "diminished circulation of the blood in the liver and consequent abnormal defecation," these being thus increased inscription of bile into the blood. Perhaps jaundice arises in
this way, though I think it is not
very probable.

I find it very difficult, by any of
the theories given, to explain many
cases of non-obstructive jaundice. For
instance in the case of icterus occurring
after poisoned blood, or during the course
of pneumonia or of a fever, is the liver so
affected by the poisoned blood, that it
can only do half work, that it can
only secrete one or both of the bile-acids
or their salts, without being able to ex-
crete them, and they entering the cir-
culation act on the blood corpuscles;
or is the liver affected in this way and
to this extent by the state of disturbance
in the nervous system; or does the
poison in the blood (if there be one) take
the place of the bile-acids causing trans-
formation of the hæmatin into some
coloring matter resembling biliverdin, the
icterus being thus independent of the
liver. In these cases there has generally
been found some fluid in the salt-bladder,
of a lighter or darker color, which can be caused by substances abnormal or in abnormal quantities, such as leucine, tyrosine, chloro, showing that abnormal transformations had taken place.

Another very interesting class of cases is that in which jaundice arises after violent emotions. This seems sometimes to arise very rapidly. Dr. Henderson, in his Lectures on Pathology this session (1863-64) mentioned the case of a man at sea, who, in a fight, turned suddenly yellow, that his opponent immediately threw down his weapon and fled. This case is mentioned by Ferreus on the authority of Villers, who also gives another example of an able, who became jaundiced when a mad dog rushed at him. If these cases are true (and I have no reason to doubt them, except their improbability), they are I
should think quite exceptional, the icterus generally making its appear-
ance in the course of an hour or two. To what is the jaundice
to be ascribed in cases such as these? Is it caused "by interrup-
tions to the circulation of the blood through the liver, arising from the influence exer-
cted by the nerves over the calibre of the branches of the portal vein"? I do not think it is; if the portal
blood were so much diminished, there would be a proportionate
diminution of the secretion of bile or bile-acids, and it must require
a comparatively large quantity of these to produce the yellow color-
no so short a time as a few hours.
Anxiety and fear, we know, frequently
increase some secretions, as for instance
that of the kidneys and that of the
intestinal mucous membrane, diarrhea
and dysentery being common effects
of emotion. May not fear, then, act
in the same manner as the liver, secretion taking place to such an extent, as to distend the ducts, causing abnormal diffusion & inbibition of the bile into the blood. Satisfactory. This is not altogether still I think it is better than the previous explination.

On a review of the whole matter, I think we must come to the conclusion that we know very little, if anything about the production of jaundice except those cases which arise from obstruction to the secretion of the secreted bile.

Thus are many other subjects in connection with jaundice, such as its occurrence as an epidemic, and in newly-born infants, and the occasional superintention of coma and delirium. On the discussion of these time forbids me to enter, and I merely conclude this somewhat unsatisfactory dissertation.